PATENT
Docket No. 511582000800

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Daniel E. AFAR, *et al.*

Serial No.: 09/323,597

Filing Date: June 1, 1999

For: NOVEL TUMOR ANTIGEN USEFUL IN DIAGNOSIS AND THERAPY OF PROSTATE AND COLON CANCER

Examiner: Gary B. NICKOL, Ph.D.

Group Art Unit: 1642

DECLARATION OF ARTHUR B. RAITANO, Ph.D. UNDER 37 C.F.R. § 1.132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Arthur B. Raitano, Ph.D., declare as follows:

1. I am a named inventor on United States Patent Application No. 09/323,597, the patent application identified above.

2. I am a Research Scientist III; Leader, Protein Expression Group for Agensys, Inc. Agensys is the assignee of the entire right and interest in the patent application identified above. I hold a B.S. degree in biology from the University of California, Davis, and a Ph.D. in Microbiology and Immunology from the University of Arizona, Tucson. I have approximately 18 years of experience in cellular and molecular immunology. My experience includes five years of graduate research, and seven years of post-doctoral research including the raising and use of

antibodies to study signal transduction pathways in human cancers. I have six years of experience at Agensys in the generation and characterization of antibodies to cancer-associated antigens. I have authored at least 17 journal articles in the field of molecular biology and immunology. My *curriculum vitae* information is attached as Exhibit A.

3. I have reviewed the specification of the patent application identified above. I have also reviewed the pending independent claim (claim 72) of this application, which reads as follows:

> 72. A method for inhibiting the growth, viability and/or survivability of cancer cells that express the nucleotide sequence SEQ. ID. No.: 1 or the cDNA in ATCC deposit 207097 (20P1F12/TMPRSS2), the method comprising:
>
> administering to the cancer cells an antibody or fragment thereof that specifically binds to a 20P1F12/TMPRSS2 protein, thereby inhibiting the growth, viability and/or survivability of said cancer cells.

4. It is my understanding that this claim is being rejected by the United States Patent and Trademark Office on the basis that the specification does not enable a person of ordinary skill in the art to practice the invention of claim 72, that is, to make and use the invention as claimed.

5. It is my assessment as a person skilled in the field of humoral immunology and cancer biology that a person of ordinary skill in the this scientific field would be able to make and use the subject matter of claim 72. My reasoning in support of this conclusion is set forth in the following paragraphs.

6. The antigen described in claim 72, referred to as "SEQ. ID. No.: 1," is a cell surface serine protease of 492 amino acids, referred to in the application as "TMPRSS2," "20P1F12," or "20P1F12/TMPRSS2," hereinafter referred to as TMPRSS2.

7. A person of ordinary skill in the art can generate "an antibody or fragment thereof that specifically binds to a 20P1F12/TMPRSS2 protein." For example, we have successfully

generated such antibodies in our laboratory (see Example 5 of the patent application identified above) using standard technology for the development of monoclonal antibodies. One of ordinary skill can generate such antibodies from the disclosure in the patent application identified above. For example, one immunizes animals, such as mice, with proteins that contain the TMPRSS2 amino acid sequence or with cells expressing the TMPRSS2 protein and then deriving hybridomas using standard technologies including harvesting of immunized spleen cells and fusion with a myeloma partner (Harlow and Lane (1988), cited at page 14 et seq. of the application as-filed). Supernatants from fusion wells specific for TMPRSS2 are identified using standard immunological techniques, including ELISA to the immunogen, immunoprecipitation, Western blotting, flow cytometry, fluorescent microscopy, and immunohistochemistry on TMPRSS2-expressing cell lines and tissues versus non-expressing cell lines and tissues. TMPRSS2 specific hybridoma wells are then cloned and stabilized using standard techniques such as limiting dilution to isolate monoclonal hybridomas secreting the TMPRSS2-specific monoclonal antibody.

8. One can administer these antibodies by incorporating them into the growth medium or other appropriate buffer in which the TMPRSS2-expressing cells reside in for *in vitro* analyses or by injection of the monoclonal antibodies in an appropriate buffer into the tissues, blood stream, or peritoneal cavity of a mammalian animal harboring TMPRSS2-expressing cells and/or tissues.

9. In addition to identifying specific binding of the monoclonal antibody to the TMPRSS2 protein and cells expressing the TMPRSS2 protein, one skilled in the art can readily screen such antibodies for functional effects induced by the consequence of the monoclonal antibody binding; such screening is routine. Functional effects evaluated in this way include but are not limited to: growth rate, induction of apoptosis, prevention of ligand binding, changes in signal transduction, inhibition or enhancement of enzymatic activity, induction of differentiation, changes in migration and adhesion, recruitment and engagement by immune effector cells etc. There are a variety of routine and standard techniques available with well defined readouts to measure the aforementioned functional effects. These assays are also used to define the optimum dosage, timing, and route of administration.

10. One of ordinary skill in the art would be able to identify cells which express 20P1F12/TMPRSS2 as follows: Use of standard RNA expression analysis procedures, including, but not limited to Northern blotting, RT-PCR, and in situ hybridization techniques with TMPRSS2 specific probes. Alternatively, by use of standard protein expression analysis procedures including, but not limited to immunohistochemistry, Western blotting, immunoprecipitation, MALDI and mass spectrophotometry techniques. Each of these techniques are routine and well known in this scientific field as of the filing of the present application in June 1999.

11. It is a scientifically reasonable expectation that engagement of a protein with an antibody specific for that protein would elicit a functional consequence (such as those outlined above in paragraph 9) that includes, but is not limited to one or more of the following: growth inhibition, blocking of enzymatic activity, induction of apoptosis, differentiation, changes in signal transduction, recruitment of immune effector cells (ADCC), changes in migration or adhesion, etc., all of which would inhibit the growth viability and/or survivability of cancer cells that express TMPRSS2.

12. I understand that the Patent Office is focusing the meaning of this claim solely on therapy. However, there are uses for the claimed method other than treatment. For example, an important activity covered by the claim is characterization of a cancer cell based on the effect elicited upon administration of an antibody that binds to it. For example, the cells may be altered in growth rate, induction of apoptosis, prevention of ligand binding, changes in signal transduction, inhibition or enhancement of enzymatic activity, induction of differentiation, changes in migration and adhesion, recruitment and engagement by immune effector cells etc. Any of these listed effects can inhibit the cell; the inhibition can inhibit the growth, viability and/or survivability of the cell. Thus, such characterization under the claimed method allows one to both characterize the cells bound by antibodies as well as to screen antibodies for antibody most effective at inhibiting growth viability and/or survivability.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Executed this 18th day of November 2003, at Santa Monica, California.

Arthur B. Raitano, Ph.D.

CURRICULUM VITAE

Arthur Bartholomew Raitano

Agensys, Inc. Santa Monica, California

Education:

Bachelor of Science, Biology	1984	University of California at Davis Davis, California
Doctor of Philosophy, Microbiology and Immunology	1991	University of Arizona, Tucson, Arizona

Experience:

1983-1985	Hospital Operating Room Assistant II, University of California, Davis, Medical Center.
1986-1987	Graduate Research Assistant II, Dept. of Microbiology and Immunology, University of Arizona. Advisor: Dr. Murray Korc.
1990-1991	Postgraduate Researcher, with Dr. Murray Korc Dept. of Medicine, University of California, Irvine.
1991-1993	Postdoctoral Fellow, with Dr. B.J. Wisnieski, Dept. of Microbiol. and Molec. Genetics, University of California, Los Angeles.
1993-1996	Postdoctoral Fellow, with Dr. Charles Sawyers, Dept. of Medicine, Div. of Hematology and Oncology, University of California, Los Angeles.
1996-1997	Assistant Researcher, with Dr. Charles Sawyers, Dept. of Medicine, Div. of Hematology and Oncology, University of California, Los Angeles.
1997-1998	Staff Scientist, UroGenesys, Inc., Santa Monica, California.
1998-2001	Research Scientist I, UroGenesys/Agensys, Inc. Santa Monica, California
2001-2003	Research Scientist II, Group Leader Protein Expression, Agensys, Inc. Santa,Monica, California
2003-present	Research Scientist III, Group Leader Protein Expression, Agensys, Inc. Santa Monica, California

Fellowship Awards Received:

- NIH Predoctoral Trainee, University of Arizona Cancer Biology Training Grant Program, 1986-1990.
- NIH Postdoctoral Trainee, UCLA Atherosclerosis Training Grant Program, 1991-1993.
- NIH Postdoctoral Trainee, UCLA Tumor Cell Biology Training Grant Program, 1993-1994.
- Jaye Haddad/Concern Foundation Fellowship in Tumor Immunology, 1994.
- UCLA Jonsson Comprehensive Cancer Foundation Fellowship, 1994-1995.

Publications:

1. Scuderi, P., K.E. Sterling, **A.B. Raitano**, T.M. Grogan and R.A. Rippe. 1987. Recombinant interferon gamma stimulates the production of human tumor necrosis factor *in vitro*. J. Interferon Res. 7:155-164.

2. Scuderi, P., R.A., Rippe, **A.B. Raitano** and J. Rybski. 1989. Human sera and culture supernatants from human tumors and diploid fetal fibroblasts suppress tumor necrosis factor secretion *in vitro*. J. Leuk. Biol. 46:34-40.

3. Scuderi, P., R.T. Dorr, J.P. Liddil, P.R. Finley, T. Meltzer, **A.B. Raitano** and J. Rybski. 1989. Alpha-globulins suppress human leukocyte secretion of tumor necrosis factor. Eur. J. of Immunol. 19:939-942.

4. **Raitano, A.B.,** P. Scuderi and M. Korc. 1990. Binding and biological effects of tumor necrosis factor and gamma interferon in human pancreatic carcinoma cells. Pancreas 5:267-277.

5. **Raitano, A.B.,** P. Scuderi and M. Korc. 1990. Long term effects of tumor necrosis factor and gamma interferon in human pancreatic carcinoma cells. Int. J. of Pancreatology 6:109-118.

6. **Raitano, A.B.** and M. Korc. 1990. Tumor necrosis factor upregulates gamma interferon binding in a human carcinoma cell line. J. Biol. Chem. 265:10466-10472.

7. **Raitano, A.B.,** P. Scuderi and M. Korc. 1991. Upregulation of gamma interferon binding by tumor necrosis factor and lymphotoxin: disparate potencies of the cytokines and modulation of their effects by phorbol ester. J. Interferon Res. 11:61-67.

8. **Raitano, A.B.** and M. Korc. 1993. Growth inhibition of a human colorectal carcinoma cell line by IL-1 is associated with enhanced expression of IFN-Y receptors. Cancer Res. 53:636-640.

9. **Raitano, A.B.,** J. Halpern, T.M. Hambuch, and C.L. Sawyers. 1995. The Bcr-Abl leukemia oncogene activates Jun kinase and requires Jun for transformation. Proc. Natl. Acad. Sci. 92:11746-11750.

10. Dickens, M., J. Rogers, J. Cavanagh, **A. Raitano**, Z. Xia, J. R. Halpern, M. E. Greenberg, C. Sawyers and R.J. Davis. 1997. A cytoplasmic inhibitor of the JNK signal transduction pathway. Science, 277:693-696.

11. **Raitano, A.B.**, Y. Whang and C.L. Sawyers. 1997. Signal transduction by wild-type and leukemogenic Abl proteins. Biochem. Biophys. Et. Acta, 1333:F201:216.

12. Xu FH, Sharma S, Gardner A, Tu Y, **Raitano A**, Sawyers C, and Lichtenstein A. 1998. Interleukin-6-induced inhibition of multiple myeloma cell apoptosis: support for the hypothesis that protection is mediated via inhibition of the JNK/SAPK pathway. Blood. 92:241-251.

13. Hubert RS, Vivanco I, Chen E, Rastegar S, Leong K, Mitchell SC, Madraswala R, Zhou Y, Kuo J, **Raitano AB**, Jakobovits A, Saffran DC, and Afar DE. 1999. STEAP: a prostate-specific cell-surface antigen highly expressed in human prostate tumors. Proc Natl Acad Sci U S A. 96:14523-14528.

14. Neshat MS, **Raitano AB**, Wang HG, Reed JC, and Sawyers CL. 2000. The survival function of the Bcr-Abl oncogene is mediated by Bad-dependent and -independent pathways: roles for phosphatidylinositol 3-kinase and Raf. Mol Cell Biol. 20:1179-1186.

15. Gu Z, Thomas G, Yamashiro J, Shintaku IP, Dorey F, **Raitano A**, Witte ON, Said JW, Loda M, and Reiter RE. 2000. Prostate stem cell antigen (PSCA) expression increases with high gleason score, advanced stage and bone metastasis in prostate cancer. Oncogene. 2000 Mar 2;19(10):1288-1296.

16. Saffran DC, **Raitano AB**, Hubert RS, Witte ON, Reiter RE, and Jakobovits A. 2001. Anti-PSCA mAbs inhibit tumor growth and metastasis formation and prolong the survival of mice bearing human prostate cancer xenografts. Proc Natl Acad Sci U S A. 98:2658-2663.

17. Afar DE, Vivanco I, Hubert RS, Kuo J, Chen E, Saffran DC, **Raitano AB**, Jakobovits A. 2001. Catalytic cleavage of the androgen-regulated TMPRSS2 protease results in its secretion by prostate and prostate cancer epithelia. Cancer Res. 61:1686-1692.